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Successful management of gamma-hydroxybutyrate (GHB) withdrawal using baclofen as a standalone therapy: A Case Report

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Abstract

Background: Gamma-Hydroxybutyrate (GHB) - a GABA-B agonist - can lead to a use disorder, and a withdrawal syndrome similar to that of alcohol. At present, evidence is lacking for how to best manage GHB withdrawal, and often clinicians rely on alcohol withdrawal management approaches, using medications like benzodiazepines (BZD). However, BZD doses needed to control GHB withdrawal symptoms are typically much higher than those required for alcohol, posing significant safety risks. Novel approaches include the use of baclofen as an adjunct to BZD, allowing for reductions in BZD requirements. While the use of baclofen as monotherapy may result in even greater risk reductions, research to support this approach is limited.

Case: We present a case of a 26-year-old female with severe GHB use disorder and history of severe withdrawal symptoms, whose withdrawal was successfully managed using baclofen alone.

Conclusion: In keeping with other case reports, baclofen appears to have potential to be used in the management of GHB withdrawal. Here, we presented a case of severe GHB withdrawal which was managed solely by baclofen. Clinical research is needed to evaluate baclofen's potential as a standalone treatment for GHB withdrawal.

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Conflicts of interest

None.

Consent

Written consent was obtained from the patient.

Keywords

Gama-Hydroxybutyrate; Baclofen; withdrawal; detoxification; gamma butyrolanctone; 1,4-butanediol

INTRODUCTION

Gamma-hydroxybutyrate (GHB) is a low molecular weight fatty acid produced naturally in the body as a metabolite and precursor of gamma-aminobutric acid (GABA) neurotransmitter. Although it has a dose-dependent (Kaupmann et al. 2003, Busardò and Jones 2015, Liechti et al. 2016), GHB is typically classified among central nervous system depressant substances with sedative hypnotic effects such as alcohol, barbiturates and benzodiazepines (BZD) (Busardò and Jones 2015, Liechti et al. 2016).

Available data indicate that GHB is used non-medically in youth and other populations such as night clubbers and men who have sex with men for its euphoric, sedative, and stimulant pro sexual effects (European Monitoring Centre for Drugs and Drug Addiction 2017). The exact prevalence of non-medical use of GHB is not known due to the absence of systemic reporting systems. In addition, unregulated substances with industrial applications such as gamma-butyrolanctone (GBL) and 1,4-butanediol (BD) have been used widely because they can rapidly change into GHB in the body (Busardò and Jones 2015). According to European drug reports, the prevalence of non-medical use of GHB varies between 0.1–1.6% and up to 28% in various subgroups (European Monitoring Centre for Drugs and Drug Addiction 2008, European Monitoring Centre for Drugs and Drug Addiction 2017, Miro et al. 2017), although the exact prevalence is not known due to absence of systemic reporting systems.

Studies in humans and animals have shown that GHB use of three to six times per day can rapidly increase tolerance and lead to physical dependence within days to weeks (Goodwin et al. 2011, Kamal et al. 2016b). GHB cessation can provoke life threatening withdrawal symptoms such as seizures and delirium with hemodynamic instability which may need to be treated in a monitored setting (Miotto K. 2001). To date, GHB withdrawal has been managed with BZD as a standard of care and a first line medication in the same manner that it is used for alcohol detoxification (Tarabar and Nelson 2004). This approach has fostered challenges including high tolerance to BZD in GHB users and requirement of large and frequent doses of BZD mandating medical monitoring (Miotto K. 2001).

Given these therapeutic challenges, baclofen, a GABA-B receptor agonist with medicinal use as an anti-spasticity agent and a muscle relaxant, has been suggested as an adjunct to BZD in the treatment of GHB withdrawal (LeTourneau et al. 2008, Lingford-Hughes et al. 2016). Available data suggest that the use of baclofen as adjunct therapy to BZD results in decreased need for BZD, and consequent decreased risk of respiratory depression and addiction potential. While using baclofen as standalone therapy may result in even greater risk reductions, to our knowledge there are no reports on the use of baclofen alone in this context. We present a case of a 26-year-old female with severe GHB use disorder and history of severe withdrawal symptoms whose withdrawal was successfully managed using baclofen alone.

CASE PRESENTATION

A 26-year-old female with a history of drinking 150 ml of GHB and smoking 1.75 gr of methamphetamine on a daily basis in the last 1.5 years was admitted to an inpatient detoxification facility in Vancouver, BC in July 2017. Apart from her GHB and methamphetamine use disorders, other relevant medical history included past alcohol use, as well as bipolar and major depressive disorders. Patient's current medications included venlafaxine, trazodone, and amitriptyline. This was the patient's fourth admission for GHB detoxification within a six-month period. On previous admissions, she had had significant agitation, anxiety and tremors which had not responded substantially to BZD. During the last admission, the patient even experienced a witnessed seizure while treated with both diazepam and phenobarbital. Therefore, during the last admission it was decided to add baclofen as an adjuvant to BZD. The dosages of 30 to 80 mg were administered to control the patient's withdrawal symptoms.

Given the limited response of the patient's withdrawal symptoms to BZD in previous admissions, alongside the suggested benefit of baclofen in the most recent admission for GHB withdrawal, in the present admission, it was decided to manage her symptoms mainly with baclofen (McLean M, personal communication). The patient was assessed hourly by a trained nurse under the "revised clinical institute withdrawal assessment for alcohol (CIWA-Ar)" protocol. Although CIWA-Ar has not been validated to be used for GHB withdrawal assessment, the team decided to use this tool due to the familiarity of the nurses with it. It was also agreed that diazepam and phenobarbital would be used in the case of lack of response to baclofen.

At the time of admission, the patient did not show any signs or symptoms of intoxication or withdrawal. However, shortly after the admission, the patient reported severe anxiety, and commenced with severe tremors, restlessness, and agitation. All the symptoms and signs significantly improved with an initial dose of 30 mg of baclofen. On day one and two, the patient received a total of 130 mg each day (scheduled doses of 20–40 mg every 4 hours (q4h) in addition to "as needed" doses of 20–40 mg q4h orally) with subsequent dose reduction to 90 mg daily on day three and four (e.g., 20–40 mg q6h in addition to the same "as needed" doses orally). On day four, the patient reported to be very comfortable and her symptoms were completely resolved with no objective signs of withdrawal. Therefore, the care team decided to taper baclofen on day five to 40 mg (10 mg q6h), and a further reduction by 10 mg daily. She received 30 mg on day six and 20 mg on day seven. There were no requirements of diazepam or phenobarbital at any time during her admission. Likewise, there were no significant baclofen side effects, with only mild drowsiness after the baclofen administration. The detoxification process was completed over seven days, after which the patient was discharged with no prescription for baclofen.

DISCUSSION

We have described a case of a 26-year-old female with a history of severe GHB use disorder, and withdrawal symptoms refractory to BZD, whose present withdrawal syndrome was successfully managed using baclofen as stand-alone therapy over seven days, without any

need of BZD or phenobarbital. It is worth mentioning that the patient's present withdrawal syndrome may have been aggravated by her comorbid methamphetamine use disorder. Indeed, a recent study found that co-use of stimulants can cause an add-on effect on GHB withdrawal manifestations, including more intense and prolonged muscle twitching, agitation and restlessness (Kamal et al. 2016a).

The standard of care for managing GHB withdrawal involves using BZD in a similar protocol as for alcohol withdrawal (Tarabar and Nelson 2004, Kamal et al. 2017). An issue with using BZD for the management of GHB withdrawal is the need for high doses given their low efficacy in this context, which in turn results in increased risk of adverse events, and consequent need for close monitoring (Miotto K. 2001, Schep et al. 2012) For example, Craig and Gomez reported a case that required an equivalent total dose of 2,655 mg of diazepam over the course of almost four days of a GHB detoxification (Craig et al. 2000).

Due to the challenges in managing GHB withdrawal, other medications have been commonly used in conjunction with or substituted for BZD, including anticonvulsants, barbiturates, valproic acid, carbamazepine and gabapentin (McDaniel and Miotto 2001, Schep et al. 2012), and even pharmaceutical GHB (Craig et al. 2000, LeTourneau et al. 2008, Lingford-Hughes et al. 2016). However, none of these approaches have shown consistent good outcomes.

More recently, there has been increasing interest in exploring the use of baclofen in conjunction with BZD for the management of GHB withdrawal, given a growing body of literature demonstrating the efficacy and safety of this approach in the context of alcohol withdrawal (LeTourneau et al. 2008, Lingford-Hughes et al. 2016). Both baclofen and GHB are GABA-B agonists, and preclinical evidence supports the potential of baclofen for the management of GHB withdrawal. For example, Smith et al. demonstrated that GABA-B receptors have greater role in the behavioural effects of GHB than GABA-A receptors (Smith et al. 2006). In this study, baclofen effects on chronic GHB use in rats were compared to the BZD flunitrazepam (i.e., a GABA-A receptor agonist) effects. In another study, Fattore et al. showed that administration of baclofen reduced GHB self-administration and GHB seeking behaviour in mice (Fattore et al. 2001). While limited, human data also supports a potential role of baclofen for GHB withdrawal management. LeTourneau et al. described the case of a 61-year-old patient with GHB withdrawal who experienced witnessed seizures despite treatment with lorazepam combined with pharmaceutical GHB (LeTourneau et al. 2008), whose symptoms improved within hours of administration of 20 mg of baclofen.

We presented a case of severe GHB withdrawal which was managed solely with baclofen. To our knowledge, this is the first case report of successful management of GHB withdrawal with baclofen alone. Given its pharmacodynamic similarities to GHB, and better safety profile compared to BZD, the use of baclofen as monotherapy for the management of GHB withdrawal is appealing. Further research is warranted to evaluate baclofen's potential as a standalone treatment for GHB withdrawal.

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